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- News & Analysis

Malaria

Vaccine Trial Meets Modest Expectations, Buoys Hopes

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Promising jab.

A baby receives a dose of the experimental malaria vaccine at a trial site in Kilifi, Kenya.

CREDIT: JOSEPH OKANGA/REUTERS

Sometimes just meeting expectations is a major achievement. Initial, eagerly awaited results from the world's first large-scale trial of a malaria vaccine, carried out at 11 sites in seven African countries, show that it reduced episodes of the disease by about half in babies and toddlers. That confirms the efficacy seen in earlier, much smaller trials of the experimental vaccine, so far the only one to show significant benefit against malaria in real-world settings.

The new findings keep the candidate on track to become the first licensed vaccine against the disease, says Christopher Plowe, a malaria vaccine expert at the University of Maryland School of Medicine in Baltimore, who is not involved in the trial. Even a partially effective vaccine, used in combination with other tools like bed nets, could curtail malaria's massive death toll

significantly, experts say. But the vaccine will be expensive by developing-world standards, and its cost-effectiveness is yet to be determined.

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Long-term investment.

Joe Cohen of GSK Biologicals has been working on the RTS,S vaccine for 24 years.

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“I am thrilled,” says Joe Cohen, one of the vaccine's original developers and leader of the malaria vaccine project at GlaxoSmithKline (GSK) Biologicals in Rixensart, Belgium. The fact that the huge trial confirms results from smaller predecessors is “fabulous,” he says. Robert Newman, head of the World Health Organization's (WHO's) malaria program, agrees. “The results are in line with what we expected. But one fears they won't hold up, so ‘in line’ is very encouraging.”

The first round of results was published online on 18 October by *The New England Journal of Medicine*; they were also announced by Bill Gates—who called them “phenomenal”—at a Seattle meeting hosted by the Bill & Melinda Gates Foundation, which has given more than $200 million to support trials of the vaccine. The data show that in 6000 children aged 5 to 17 months, three doses of the vaccine cut the risk of any episode of malaria by 56% and the risk of severe disease by 47%. That's far from the 90% efficacy that most vaccines against viral and bacterial disease achieve. But the *Plasmodium falciparum* parasite, with its multiple life stages, is a much more difficult target, and no one expected a first-generation vaccine to be more than partially effective. “This vaccine will not be a magic bullet against what is a very, very difficult disease,” Cohen says. “It is one weapon to be added to an arsenal of other interventions.”

The vaccine, called RTS,S, was developed in 1987 by researchers working for a predecessor to GSK Biologicals. It contains an engineered protein that combines a protein fragment from *P. falciparum* and a protein from the hepatitis B virus that helps trigger a strong immune response. The vaccine is designed to block the parasite's ability to infect the liver and mature there.

After early human trials in 1997 showed promising results—protecting six of seven adult volunteers—GSK entered a public-private partnership with the PATH Malaria Vaccine Initiative (MVI) to further develop the vaccine. The first field trials in 2000 children in Mozambique, launched in 2003, showed that the vaccine lowered the risk of developing malaria symptoms by 30%, with no severe side effects (*Science*, 22 October 2004, p. 587). Since then, phase II trials in Mozambique, Kenya, and Tanzania have consistently shown that the vaccine can cut the number of malaria episodes by between 35% and 53% (*Science*, 12 December 2008, p. 1622).

The phase III trial—the final test—enrolled more than 15,000 babies aged 6 to 12 weeks and toddlers between 5 and 17 months across sub-Saharan Africa. All were scheduled to receive three doses, each 1 month apart; a subgroup will receive a booster dose 18 months later. The results announced this week are for the toddlers and cover the 12 months after their first shot. (Infants were enrolled slightly later, so results from that group won't be available until the end of 2012.) Children who missed one or two of the doses were almost as well protected as those who received all three shots, the researchers report.

The vaccine also looks fairly safe. Children who received the vaccine had a slightly higher rate of seizures than those who received the control injection, a rabies vaccine. But the independent safety board that keeps watch over the trial has not raised any concerns, says MVI Director Christian Loucq. Children enrolled in the trial had a very low risk of dying from malaria—even if they received the control injections—mainly because clinics put in place procedures to detect and treat cases as soon as possible. There were only 10 malaria deaths in the first 2 years of the study, Cohen says.

In a separate analysis, the researchers looked at the rate of severe malaria to date in all 15,460 children enrolled in the study; they found that the vaccine reduced the rate of severe, life-threatening disease by 35%. That hints that effectiveness might be lower in the babies, but Loucq and Cohen caution that the number is very preliminary.

The babies received their doses at the same time they receive the standard infant vaccinations recommended by WHO. Adding the malaria vaccine to existing vaccination schedules would be the most practical approach if the vaccine is to be widely used, and smaller-scale trials have suggested that it is effective and safe when given along with the other shots.

The trial will continue until 2014 and will follow the children until 30 months after their third dose. Once the full results are unblinded, researchers will know more about how long protection lasts and will also be able to compare the vaccine's performance at different study sites, which have different rates and seasonal patterns of malaria trans mission. That could help governments and public health experts decide where RTS,S might have the most impact. The complex vaccine is expensive to make, and its cost-effectiveness is a major issue, says Scott Filler of the Global Fund to Fight AIDS, Tuberculosis and Malaria. “The key question is going to be cost,” he says, given the limited funds available for fighting malaria.

GSK, which has invested more than $300 million in RTS,S to date, has pledged to keep the price as low as possible—just manufacturing costs plus a small return to be reinvested in development of second-generation malaria vaccines or vaccines against other neglected tropical diseases. Even

so, a full vaccine course is likely to cost more than other prevention methods, such as insecticide-treated bed nets, which also offer partial protection. Many countries have already rolled out massive net distribution projects, and 75% of the children in the trial slept under a net, Cohen says; the results show that the vaccine can provide an extra layer of protection on top of the nets, he says.

WHO is expected to take all such issues into account when it drafts policy recommendations for use of the vaccine after the trial's final results come in. The vaccine has “incredible potential” to reduce suffering, Filler says, but deciding how and where to use it will take much more work. “These are going to be incredibly challenging questions for which we—the community as a whole—don't have answers yet.”